

Clinical features and surgical treatment of chronic pancreatitis with symptoms of biliary hypertension

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Key words: chronic pancreatitis, biliary hypertension, biliary pressure, magnetic resonance cholangiopancreatography, duodenum-preserving resection

Chronic pancreatitis (CP) is a progressing disease with repeated aggravations of chronic inflammations, development of sclerosis and fibrosis leading to the replacement of the secretory tissue of the gland by connective tissue and decrease of the exocrine function of the pancreas [1].

In cases of CP, anatomical contact of the pancreas with adjacent organs facilitated the development of extrapancreatic complications, like duodenal abevacuation, biliary hypertension (BH), thrombosis or extravascular compression of splenoportomesenteric confluence [5].

Surgical treatment is required by 4 to 9% of patients with CP [2]. The performance of surgical intervention is justified when there are clinical signs of CP and morphological changes in the pancreas where conservative therapy is inefficient and there is a threat of CP complications or if these complications have already occurred [2]. The tasks of surgical treatment of CP include elimination of pain and local complications, preservation and improvement of exocrine and endocrine functions of the pancreas, and improvement of the patients' quality of life [10].

According to H. Beger and M. Buchler [6], occurrence of such CP complications as stenosis of the common bile duct (CBD) (59.6%) and duodenum (36.4%), and portal hypertension (17.7%) are indications to apply the isolated resection of the pancreas head (Beger's procedure). According to the Resolution of the Plenary Session of the Board of the Hepato-Pancreato-Biliary Association of Russia and the CIS (Izhevsk 19-20 April 2012) [4], «...Biliary hypertension occurs in 30-50% of patients with CP, it is often asymptomatic, accompanied by a

temporary increase of levels of bilirubin and alkaline phosphatase. Before operating on such patients, it is necessary to obtain the information about the length of the diminution of the distal section of hepaticocholedochus. For this purpose, it is necessary to perform ERCP (if necessary, direct contrasting of bile ducts should be accompanied by biliary decompression) or MRCP. In cases of longitudinal stenosis of the distal section of hepaticocholedochus, it is expedient to supplement duodenum-preserving resection of pancreas head by application of hepaticojejunostomy. Biliopancreatic connection in the area of pancreas head should be done only when you are confident that the area of choledoch above the resected pancreas head is permeable. Biliary complications that take place in 2-8% of patients after the resection interventions, including ones with the application of biliopancreatic anastomosis, prove the topicality of this issue and require further accumulation of experience.”

Objective: To study the patterns of clinical course and surgical treatment of patients who have CP with signs of BH.

Materials and methods of research. We analyzed the results of surgical treatment of 49 patients with CP complicated by BH who underwent surgical treatment at the department of surgery at the Ivano-Frankivsk Regional Clinical Hospital in 2009-2015. In 15 (30.6 %) patients, BH was combined with chronic duodenal obstruction (CDO), and in 4 (8.1%) patients, a combination of BH+CDO and local venous hypertension (VH) of vessels of the pancreaticobiliary area was found. There were 45 (91.9%) men and 4 (8.1%) women aged from 21 to 72. The patients were divided into two groups. In 14 (28.5 %) patients (1st group), BH was diagnosed based on anamnesis, data of clinical, laboratory (level of general and conjugated bilirubin, alkaline phosphatase), and instrumental methods (ultrasonography (USG), endoscopic retrograde cholangiopancreatography (ERCP), computed tomography (CT), magnetic resonance retrograde cholangiopancreatography (MRCP), as well as by intraoperative monitoring of biliary pressure using the developed device [3]. In 35 (71.5 %) patients (2nd

group), BH was diagnosed based on the anamnesis, data of clinical, laboratory and instrumental methods, without the intraoperative monitoring of biliary pressure.

Results and their discussion.

Main typical complaints of patients with CP accompanied by BH included pain and jaundice. Pain syndrome occurred in 47 (95.9%) of patients. In 39 (82.9 %) of patients, the pain was permanent, and increased during food intake; in 8 (17.1%) patients, the pain was recurring and cramp-like. In 40 (85.1%) patients, the pain focalized in the pit of the stomach, in 3 (6.4%) – in the left hypochondrium, and in 4 (8.5%) – in the right hypochondrium. In 22 (46.8%) patients, the pain irradiated into the back or was of belt-like nature. Twenty-nine (61.7 %) patients used painkillers, including the potent ones, all the time; 18 (38.3%) patients - occasionally. The pain syndrome in cases of CP with BH was caused by fibrous-degenerative changes in the head of the pancreas with the involvement of the nervous apparatus and duct system of the gland into the pathological process.

Jaundice (icteritiousness of skin and visible mucous coat) occurred only in 27 (55.1%) patients with CP accompanied by BH. In 11 (40.7%) patients, the jaundice was recurrent. The other patients with BH had no jaundice at all.

Weight and body mass loss was found in 41 (83.6%) patient, particularly, a weight loss of up to 5 kg – in 24 (58.5%) patients, from 5 to 10 kg – in 15 (36.6%) patients, and more than 10 kg – in 2 (4.9%) patients.

In 33 (67.3 %) patients, a manifest dyskinetic syndrome (diarrhea, constipations) took place. Dyspeptic syndrome (appetite change, nausea, vomiting that brings no relief, aversion to greasy food, and flatulence) were found in all patients. Such manifestations of the disease induced 39 (79.6%) patients to take enzymatic agents regularly. Thirty-one (63.3 %) patient had a manifest asthenovegetative syndrome (general weakness, irritability, sleep disorder, performance decrement).

Table 1

Clinical symptoms in patients with CP accompanied by BH

Clinical signs	Groups of patients	
	1 st group (with monitoring of biliary pressure) (n=14)	2 nd group (without monitoring of biliary pressure) (n=35)
Pain syndrome	13 (92.8 %)	34 (97.1 %)
Jaundice	8 (57.1 %)	17 (48.5 %)
Weight loss	10 (71.4 %)	31 (88.6 %)
< 5 kg	6 (42.8%)	18 (51.4 %)
5-10 kg	4 (28.6 %)	13 (37.1 %)
>10 kg	-	2 (5.7 %)
Dyskinetic syndrome	6 (42.8 %)	27 (77.1 %)
Dyspeptic syndrome	14 (100 %)	35 (100 %)
Asthenovegetative syndrome	7 (50 %)	28 (80 %)

The palpatory examination was of little importance for diagnostics of CP accompanied by BH; it stated a different degree of painfulness in the upper part of the abdomen.

Among all the laboratory examinations, of importance for diagnostics of CP with BH was the determination of the levels of total and conjugated bilirubin in the blood serum, as well as alkaline phosphatase. The increase in the level of total bilirubin at the cost of direct fraction indicated to the mechanical character of jaundice. Hyperbilirubinemia was found in 33 (67.4%) patients, in 6 of them, this indicator exceeded 200 micromole/l. The diagnostic value of the level of alkaline phosphatase as a marker of cholestatic states in our research was insignificant. Hyperphosphatasemia occurred in 21 (42.8%) patients.

Thus, it was possible to diagnose biliary hypertension on the basis of clinical laboratory data (icteritiousness of skin and mucous coat, hyperbilirubinemia) only in 33 (67.4%) patients.

All patients with BH had a USG. It revealed an enlarged and indurated head of the pancreas (from 3.5 cm to 5.3 cm). Dilation of bile passages (from 0.7 cm to 1.7 cm) was diagnosed in 33 (67.4%) patients.

ERCP was applied in 12 (22.4%) patients with CP accompanied by BH. A manifest tubular stenosis of the common bile duct was diagnosed in 11 (91.6%) patients. In four patients, the examination ended by endobiliary stenting; choledocholithiasis was found in one patient (8.3%) who underwent consequent papillosphincterotomy and lithoextraction.

CT was done in 34 (69.4%) cases of CP accompanied by BH. In the course of the examination, their heads of the pancreas were found to be enlarged and indurated. In three patients, CT allowed diagnosing cysts in the head of the pancreas. Suprapancreatic dilation of bile ducts was found in 26 (74.4%) patients. In diagnostics of biliary hypertension, USG and CT conclusions coincided in 10 (10/14; 71.4 %) patients of the first group and pertained to the cases with manifest dilatation of bile ducts. In three patients, CT determined the signs of cholangitis (gas in the common bile duct with a manifest walls edema) secondary to biliary hypertension; USG failed to show specific data of cholangitis in these patients.

MRCP was applied to five patients with CP accompanied by BH; tubular stenosis of the intrapancreatic part of the common bile duct and its suprastenotic dilation was found in all of them.

Separately, the interconnection between the data of instrumental methods of examination in regard to common bile duct dilation with the level of bilirubin in the blood serum was studied.

Table 2

Interconnection between the dilatation of the common bile duct and hyperbilirubinaemia in patients with CP accompanied by BH

Diameter of the common bile duct, mm	Bilirubin indicators, micromole/l			
	21-50	51-100	101-200	> 200
Up to 7 mm	4 (...%)	2 (...%)	-	-
8-10 mm	2 (...%)	8 (...%)	4 (...%)	1 (...%)
10 mm and more	-	4 (...%)	3 (...%)	5 (...%)
Total:	6 (18.2 %)	14 (42.4 %)	7 (21.2 %)	6 (18.2 %)

The analysis conducted showed a directly proportional connection between the diameter of the common bile duct and the level of bilirubin in blood. However, in six (18.2%) patients with hyperbilirubinemia, common bile duct was not dilated; and in seven patients, dilation of the common bile duct took place with normal ranges of bilirubin in the blood.

In 14 patients of the first group, we studied the interconnection between BH and the level of bilirubin in blood serum (table 3).

Table 3

Interconnection of BH and hyperbilirubinaemia

Bilirubin, micromole/l	Indicators of biliary pressure, mm w.g.			
	150 -200	201 - 251	251 - 300	over 300
21-50	1 (7.1 %)	1 (7.1 %)	-	-
51-100	1 (7.1 %)	2 (14.2 %)	1 (7.1 %)	-
101-200	-	2 (14.2 %)	1 (7.1 %)	-
> 200	-	2 (14.2 %)	2 (14.2 %)	1 (7.1 %)

The data received allowed determining a directly proportional connection between the value of biliary pressure and the level of bilirubin in blood serum. The higher is the biliary pressure, the more manifest is the hyperbilirubinemia.

Our experience of surgical treatment of 163 patients with complicated forms of CP allowed determining that BH with underlying other manifestations of CP is an absolute indication for surgical treatment. An essential condition for determining the surgical indications is a stable clinical picture and manifest pathomorphological changes in the pancreas. The progress of pathological changes in the head of the pancreas facilitates the spread of the process to the terminal division of the common bile duct with the development of tubular stenosis. The presence of concrements in the main pancreatic duct is not a reason of BH development by itself. However, Wirsung's duct lithiasis contributes to the progress of CP and appearance of other complications. Therefore, a combination of the Wirsung's duct lithiasis and BH is also an undeniable surgical indication in patients with CP.

In some cases, fibrous-degenerative changes in the head of the pancreas or pancreatic pseudotumor with signs of BH stimulated the tumorous process of the head of the pancreas. Modern laboratory and instrumental methods of examination used at the preoperative stage do not always enable full exclusion of the malignant process. Therefore, one of the surgical indications was a suspected tumorous process in the head of the pancreas.

During the preparation for surgical intervention, patients with CP accompanied by BH required complex personalized preoperative preparation. Not only pathological changes in the pancreas but also the general condition of patients, concomitant diseases, the degree of pathological changes in adjacent organs (liver, stomach, duodenum, etc.) should be taken into account.

General principles of preoperative preparation included:

- elimination of pain syndrome;
- restoration of hemostasis indicators;
- prevention of acute inflammatory changes in the pancreas;
- prevention of possible complications in regard to other organs and systems.

Perioperative management of CP patients with obstructive jaundice presupposed correction of a number of specific abnormalities related to chronic pancreatitis and complications of cholaemia.

The level of blood albumin does not reflect the patient's nutritional status. However, preoperative hypoalbuminemia (<40 g/l) has a clear correlation with postoperative complications [8, 9]. Therefore, surgical intervention was postponed by 10-14 days for correction of the nutritional status in cases where at least one of the following criteria was found: hypoalbuminemia < 30 g/l, body-weight index < 18.5 kg/m², body weight loss over 6 months exceeded 10-15 % [11]. Wherever it was impossible to apply adequate enteral feeding, parenteral feeding ("three-in-one" systems: "Kabiven" and "Oliclinomel") was used.

To prevent thromboembolic episodes in high-risk patients, low molecular weight heparins were used; the first dose was prescribed 12 hours prior to the

beginning of the surgery (which is associated with low risk of intraoperative hemorrhage). Pharmacological prevention decreases the risk of pulmonary embolism in surgical patients by 75 % [7].

It was considered that maintenance of glycemia at the level not exceeding 8-9 millimole/l during the perioperative period in patients with diabetes mellitus to be of vital importance. Over a period of several days, the patients received regular insulin only. Due to the fact that in stress conditions and in conditions of contrinsular hormones discharge (catechol amines, cortisol, growth hormone) the level of hyperglycemia may become unpredictable, we deemed it necessary to conduct a thorough monitoring of blood glucose. Prevention of acetonemia was achieved by infusion of glucose with insulin until the nutrition support was restored. We noticed that the risk of transitory hyperglycemia increased dramatically during the infusion of solutions for parenteral feeding. Administration of an additional dose of insulin into the infusion bottle/pack according to the carbohydrates content in it prevented the excessive hyperglycemia. In all cases of doubt, we made an express test to determine the glucose level, for example, using a glucometer. In our opinion, this device should be available in every surgical hospital where large-scale abdominal interventions on the pancreas are performed.

Prevention of wound infection envisaged the following: adequate oxygenation, maintenance of normothermia, normoglycemia, euvolemia, blood transfusion, if necessary, and preventive antibiotics. Administration of the first dose of antibiotic was done 30-60 min. before the incision; repeated administration was done during a prolonged surgery and large blood loss. Administration of two doses is quite acceptable during interventions on the pancreas. The interval between them depended on the half-life of the prescribed antibiotic.

Epidural analgesia was adjusted during preparation to surgery. Moreover, the combination of general anesthesia with thoracic epidural anesthesia is a method of choice in anesthetic support of the large-scale abdominal surgery. Application of epidural anesthesia/analgesia pursued the following goals: anesthetization proper (which is more effective than opioids) with an emphasis on the upper part of the

abdomen; stimulation of intestinal motility; and improvement of splanchnic perfusion. In addition, we took into account the fact that epidural analgesia decreases the frequency of occurrence of thromboembolic events, complications on the part of the respiratory system, decreases the level of catastrophic response to surgical trauma and release of stress hormones, decreases insulin resistance, and facilitates early energizing in the postoperative period. Catheterization of the epidural space was done at levels Th5-Th8. The safest local anesthetic for pre- and postoperative epidural analgesia still remains Ropivacaine (we used “Naropin” with the concentration of 2 mg/ml). Bupivacaine (“Marcaine” 0.25%) was used for intraoperative anesthesia.

Patients with obstructive jaundice required a specific approach. Obstruction of bile passages with considerable cholaemia leads to damage of important functional systems. In regard to the cardiovascular system, it may cause the decrease of myocardial contractivity, brachycardia, vasodilation with the decrease in the ability to mobilize blood from the splanchnic basin in case of a hemorrhage. The risk of intraoperative hypotension / circulatory collapse increases; sensitivity to vasoconstrictors decreases. What concerns the urinary system, the risk of acute kidney damage (lowered intravascular volume, myocardial insufficiency, the nephrotoxic influence of the circulating bile salts) increases. Finally, the level of hyperbilirubinemia correlates with the postoperative decrease of the creatine clearance. Clotting system: malabsorption of vitamin K because of bile acids and bile salts not getting into the intestinal tract leads to a reduction of procoagulant factors (II, VII, IX, X) synthesis - decrease in prothrombin ratio. Malabsorption of other fat-soluble vitamins A, D, and E increases the risk of hemorrhagic gastritis and stress ulcers and has a negative impact on the healing of the postoperative wound. Other infectious complications include: prolonged obstruction of bile passages can lead to cholangitis; lack of bile inflow into the intestinal tract promotes translocation of bacterial blood into the portal blood flow which may result in the development of sepsis. Liver dysfunction impairs albumen synthesis,

medication metabolism, and, in complicated cases, a hepatic encephalopathy may develop.

In view of the abovementioned, the patients that have biliary hypertension with underlying CP underwent during the preoperative period the following procedures:

1. Cleansing of the bile passages (under USG supervision or by endoscopic stenting) in cases of a prolonged/serious jaundice (certainly in cases of hyperbilirubinemia of over 250 micromole/l).

2. Correction of anhydration, water-electrolyte imbalance (balanced Hartman and Ringer's lactate saline solutions, glucose-potassium-insulin mixture).

3. Refraining from the prescription of hepato- and nephrotoxic medications (acetaminophen, nonsteroidal antiinflammatory drugs, aminoglycosides), as well as from using benzodiazepines with a long half-life (diazepam) in the perioperative period, and thiopental and halothan during anesthesia.

4. Refraining from the application of opioids, especially phentanyl, and morphine, for they may cause Oddi's sphincter spasm, which may aggravate biliary hypertension, as well as cause significant inaccuracies of monitoring of pressure in bile passages. Naloxone, nitrate, and atropine annihilate this effect.

5. To protect the mucous coat of the gastrointestinal tract, we used proton pump inhibitors (for example, omeprazole 20 mg BID) or H₂ receptor antagonists (famotidine 20 mg BID).

6. Treatment of cholangitis presupposed prescription of cefoperazone preparations ("Sulperazone") along with clearance of bile ducts.

7. Coagulopathy (an excessive increase of the prothrombin index / international normalized ratio) required to administrate parenteral forms of vitamin K ("Kanavit") during the preparatory stage.

8. To reduce the risk of Gram-negative bacteria translocation and prevent/reduce hepatic encephalopathy, lactulose (for example, "Duphalac" 30 ml quater in die) was used.

All patients underwent surgical treatment (table 4).

Table 4

Methods of surgical correction of biliary hypertension in patients with chronic pancreatitis

Surgery	1st group (with monitoring of biliary pressure) (n=14)	2 nd group (without monitoring of biliary pressure) (n=35)
Frey's procedure	13 (92.8 %)	10 (28.6 %)
<i>standard</i>	6	5
<i>with hepaticoenteroanastomosis (HEA)</i>	3	4
<i>including with insertion according to Kopchak and HEA</i>	3	1
<i>with excision of pancreas lingula</i>	1	-
<i>with application of biliopancreatic anastomosis</i>	-	1
pancreaticoduodenal resection (Whipple procedure)	-	5 (14.3 %)
Berne modification of Beger procedure	-	2 (5.7 %)
Longitudinal pancreaticojejunostomy	1 (7.1 %)	6 (17.1 %)
<i>with hepaticoenteroanastomosis</i>	1	3
<i>with insertion according to Kopchak and HEA</i>	-	3
Cystenterostomy	-	2 (5.7 %)
Endoscopic cystoduodenostomy		2 (5.7 %)
Palliative hepaticojejunostomy	-	2 (5.7 %)
External draining of pancreatic cyst	-	1 (2.8 %)
ERCP with endobiliary stenting	-	5 (14.3 %)

Surgeries of choice in patients with CP accompanied by signs of biliary hypertension included duodenum-preserving resections (Frey's procedure, Beger's procedure, Berne modification), which in 30% of cases required additional intervention on bile ducts (application of biliodigestive anastomoses or

biliopancreatic anastomoses in the area of pancreas head). Intraoperative monitoring of biliary pressure allowed determining non-manifest BH and choosing the right surgical treatment.

Conclusions:

1. Biliary hypertension with underlying CP can be detected using clinical laboratory examinations, USG and CT data in 74.4% of patients. The use of MRCP and intraoperative monitoring of biliary pressure supplements the complex of examinations and allows detecting non-manifest BH.

2. Preoperative preparation of patients with CP and signs of BH should take into account the changes in organs and systems of the organism connected with an abnormality of bile outflow.

3. Surgeries of choice in patients with CP and signs of biliary hypertension are duodenum-preserving resections (Frey's procedure, Beger's procedure, and Berne modification), which in 30% of cases require additional intervention on bile ducts (application of bilidigestive anastomoses or biliopancreatic anastomoses in the area of pancreas head resection).

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The article analyzes the clinical features of biliary hypertension in chronic pancreatitis and capabilities of instrumental methods for their diagnosis. The developed algorithm of pre-surgical preparation of patients with biliary hypertension takes into account changes in the organs and body systems related to the violation of the outflow of bile. Surgeries performed in patients with chronic pancreatitis with symptoms of biliary hypertension are briefly analyzed. Surgeries of choice are duodenum-preserving resections (Frey, Beger, Berne surgeries), which in 30% of cases require additional intervention on the bile ducts (application of biliodigestive or biliopancreatic anastomosis in pancreatic head resection area).